**ATTORNEY'S DOCKET NUMBER: 0092662-0032 (BWH0402; PSU 99-2076)**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Applicant: | Drazen *et al.* | Examiner: | Myers, C. |
| Serial No.: | 09/990,596 | Art Unit: | 1655 |
| Filed: | November 21, 2001 | | |
| For: | DIAGNOSING ASTHMA PATIENTS PREDISPOSED TO ADVERSE β-AGONIST REACTIONS | | |

Box Response
Assistant Commissioner for Patents
Washington, D.C. 20231

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231
on 12-20-02
Sandra Sligh

Sir:

**RESPONSE UNDER 37 CFR §1.111**

Applicant respectfully requests a three (3)-month extension of time to respond to the Office Action mailed June 20, 2002. Responsive to that Action, Applicant respectfully requests consideration of the following Remarks.

**Amendment**

Please amend claims 1, 2, 5 and 6 to read as shown below. The changes made to these claims are illustrated in Appendix A, Version with Markings to Show Changes Made. All claims that will be pending in the case after entrance of the present Amendment, in their amended form, are presented in Appendix B, Claims Pending After Entrance of Present Amendment.

Amended Claims

1. A kit comprising:

a first set of primers selected so that one of the primers hybridizes to a first portion of a human $\beta_2$-adrenergic receptor gene, which first portion includes a sequence encoding position 16 of said human $\beta_2$-adrenergic receptor, in such a manner that, when used in a polymerase chain

reaction, said first set of primers amplifies said portion when position 16 is Arg but not when position 16 is Gly; and

a second set of primers selected so that one of the primers hybridizes to a first portion of a human $\beta_2$-adrenergic receptor gene in such a manner that, when used in a polymerase chain reaction, said second set of primers amplifies said portion when position 16 is Gly but not when position 16 is Arg,

said first and second sets of primers being provided together in a container.

2. The kit of claim1 further comprising a component selected from the group consisting of: amplification buffer, water, DNA polymerase, first control DNA including a first human $\beta_2$-adrenergic receptor gene allele that encodes Arg at human $\beta_2$-adrenergic receptor position 16, second control DNA including a second human $\beta_2$-adrenergic receptor gene allele that encodes Gly at human $\beta_2$-adrenergic receptor position 16, instructions for use, and combinations thereof.

5. The kit of claim 4, wherein said sequencing primer is fluorescently labeled for use in an automated genetic analyzer.

6. The kit of claim 3 further comprising a component selected from the group consisting of amplification buffer, water, DNA polymerase, first control DNA including a first human $\beta_2$-adrenergic receptor gene allele that encodes Arg at human $\beta_2$-adrenergic receptor position 16, second control DNA including a second human $\beta_2$-adrenergic receptor gene allele that encodes Gly at human $\beta_2$-adrenergic receptor position 16, instructions for use, and combinations thereof.

**Remarks**

Claims 1-7 are pending in the present case; all of them stand rejected. Each of the rejections is addressed individually below.

Indefiniteness

Applicant thanks the Examiner for pointing out certain informalities in claims 1, 2, and 5; these informalities have been corrected by the present Amendment.

Art rejections

The Examiner has rejected claims 3-6 as anticipated by Green or Reihsaus, and all claims as obvious over Green or Reihsaus in view of the Stratagene catalog. As noted previously, Applicant does not disagree that Green teaches methods of detecting β-adrenergic receptor gene polymorphisms, including at position 16. However, the present claims recite a *kit*, which is a single container in which are contained primers appropriate and sufficient for amplification of the recited polymorphism. Nowhere does Green teach a container housing such selected primers. Green therefore cannot anticipate claims 3-6.

Furthermore, Green does not suggest any of the claimed kits. Specifically, Green does not provide any motivation to select primers that amplify position 16 sequence and to package them in a kit. Such motivation requires a demonstration that one would want to use the same primers repeatedly, so that there is a utility associated with packaging them together. The Green reference shows, with a P value of $< 0.05$, that cell lines expressing the Gly16 allele exhibit enhanced agonist-mediated downregulation of the receptor (see pg. 30 and Table 2). However, no functional differences (e.g., differences in cAMP responses) were observed between the Gly16 and Arg16 alleles. These results do not motivate repeated detection of this allele so as to indicate production of a *kit*.

First of all, while a P value of $< 0.05$ is generally considered "reliable" in a research context, it is not the standard for a diagnostic test. Applicant has offered to submit a Declaration from a large and established diagnostics company that a P value of $< 0.05$, even if it were for a meaningful factor, would not support production of a kit.

Furthermore, in this case, the P value relates to a correlation that has no functional significance. This, even if a P value of $< 0.05$ could possibly support production of a kit, it cannot in this instance. Thus, the disclosure of Green cannot render obvious the claimed

invention. The Stratagene catalog, even if it does provide descriptions of other sets of molecular biology reagents packaged as kits, adds nothing that can overcome the deficiencies of Green with respect to the present claims.

Reihsaus also cannot anticipate or render obvious the presently claimed invention. Reihsaus, like Green, fails to teach a separate container housing the recited primers and therefore cannot anticipate the claims. Reihsaus does detect a *potentially* meaningful correlation, specifically that corticosteroid use might be related (P value of $< 0.05$ or $< 0.03$, pg. 337) to the presence of the Gly16 allele. Applicant argued in a telephonic interview with the Examiner that this degree of correlation was not sufficient to establish motivation for production of a kit (i.e., for multiply repeated testing). The Examiner has rejected this argument by stating that a P value of $< 0.05$ is significant. As noted above, Applicant acknowledges that a P value of $< 0.05$ is often used as a boundary to establish minimum significance. However, such a P value does not *establish* a correlation; Applicant respectfully submits, however, that minimum significance is not sufficient to motivate production of a kit.

Applicant particularly points out that even Reihsaus recognized that the data in the paper were preliminary (and did not establish a firm correlation). The concluding sentence of the Reihsaus paper states "Interestingly, though, one mutation of this receptor *may* portend a different clinical profile and thus *may* play an accessory role in the pathogenesis of asthma" (emphasis added; page 338). At *most*, this disclosure could be said to motivate a researcher in the field to try to find a correlation that would support production of a kit. However, there would be no reasonable expectation of success. There is no indication that the Reihsaus correlation itself has held up.. The present inventors, by contrast, established a firm correlation ($P < 0.001$), supporting development and production of a diagnostic kit. The present claims are not obvious over Reihsaus. The Stratagene catalog, even if it does provide descriptions of other sets of molecular biology reagents packaged as kits, adds nothing that can overcome the deficiencies of Reihsaus with respect to the present claims.

In view of the arguments presented above, the Applicant requests that the Examiner withdraw the rejections of claims 1-7 under 35 U.S.C. §103(a).

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

Dated: 12/20/2002

Brenda Herschbach Jarrell, Ph.D.
Registration No. 39,223

Choate, Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109
(617) 248-5000